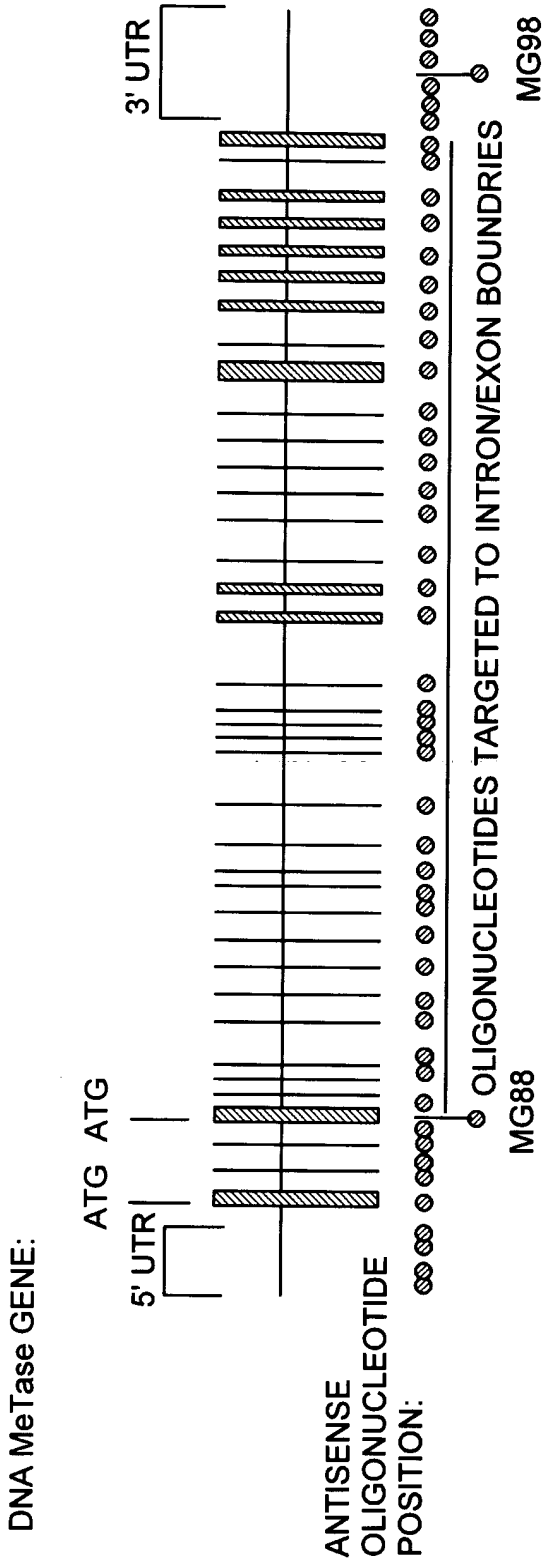


FIG. 1

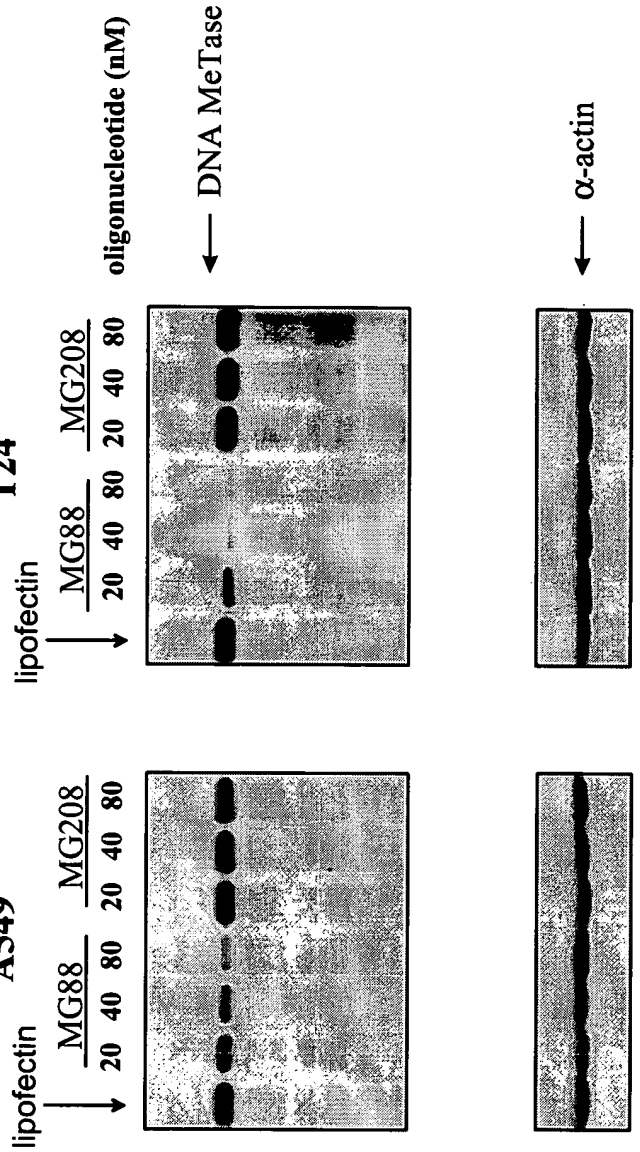

A549
T24
lipofectin
MG88
MG208
20 40 80 20 40 80
oligonucleotide (nM)
DNA MeTase
α-actin

FIG. 2

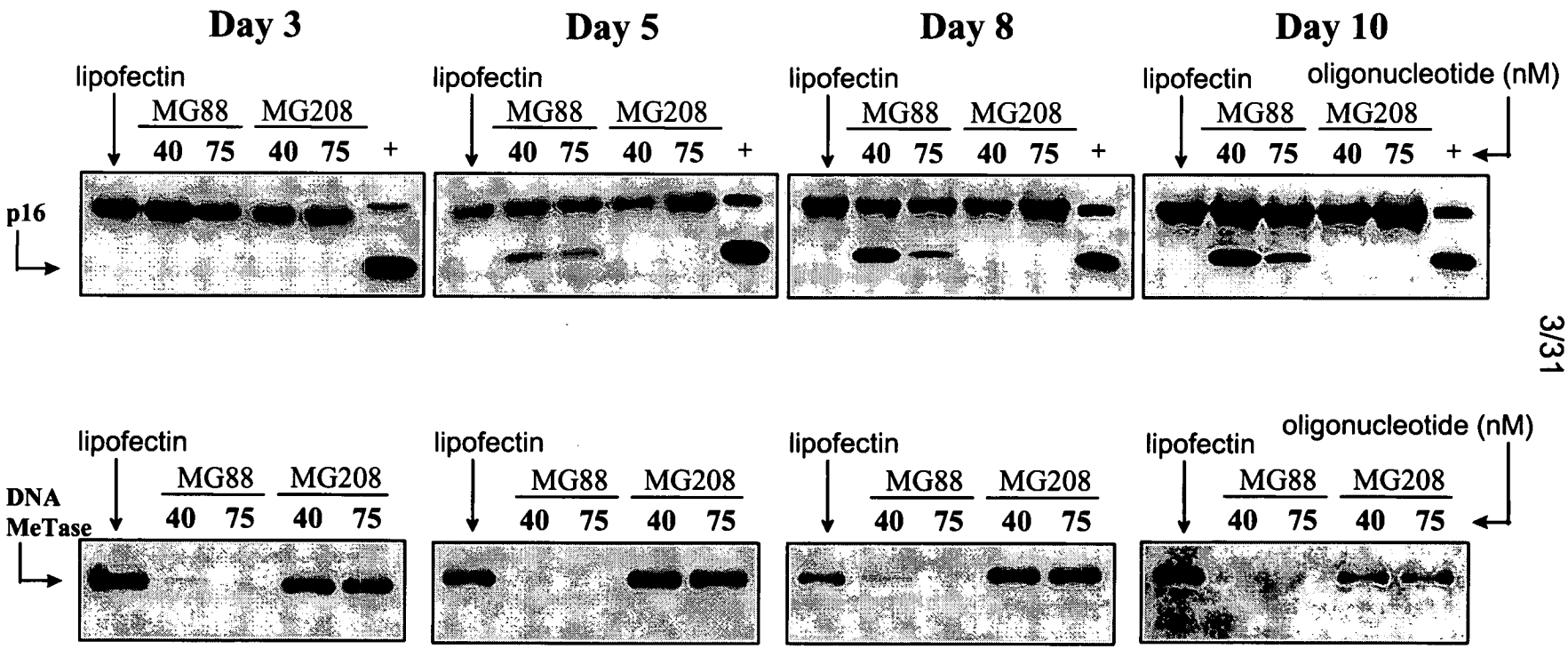

Day 3
Day 5
Day 8
Day 10
lipofectin
MG88
MG208
40 75 40 75 +
oligonucleotide (nM)
p16
DNA MeTase

FIG. 3A

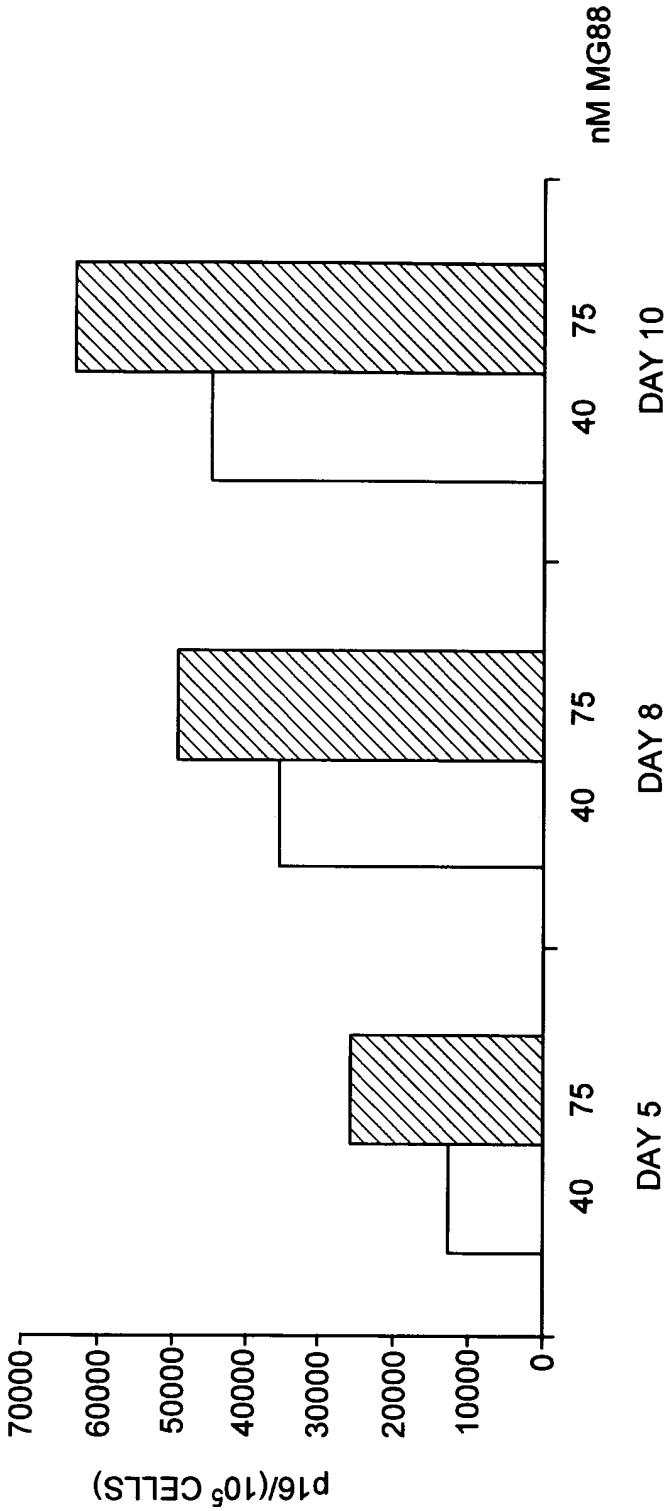

p16/(10^5 CELLS)
70000
60000
50000
40000
30000
20000
10000
0
40
75
DAY 5
40
75
DAY 8
40
75
DAY 10
nM MG88

FIG. 3B

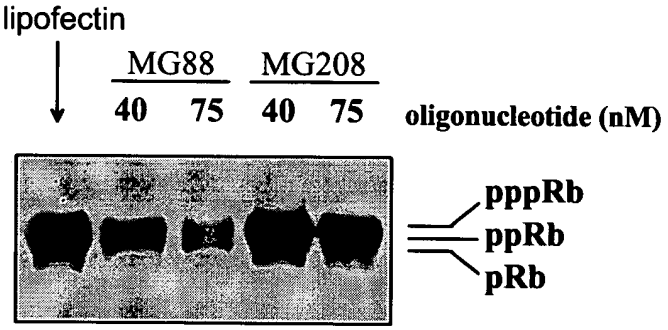

lipofectin
MG88
MG208
40
75
40
75
oligonucleotide (nM)
pppRb
ppRb
pRb

FIG. 4

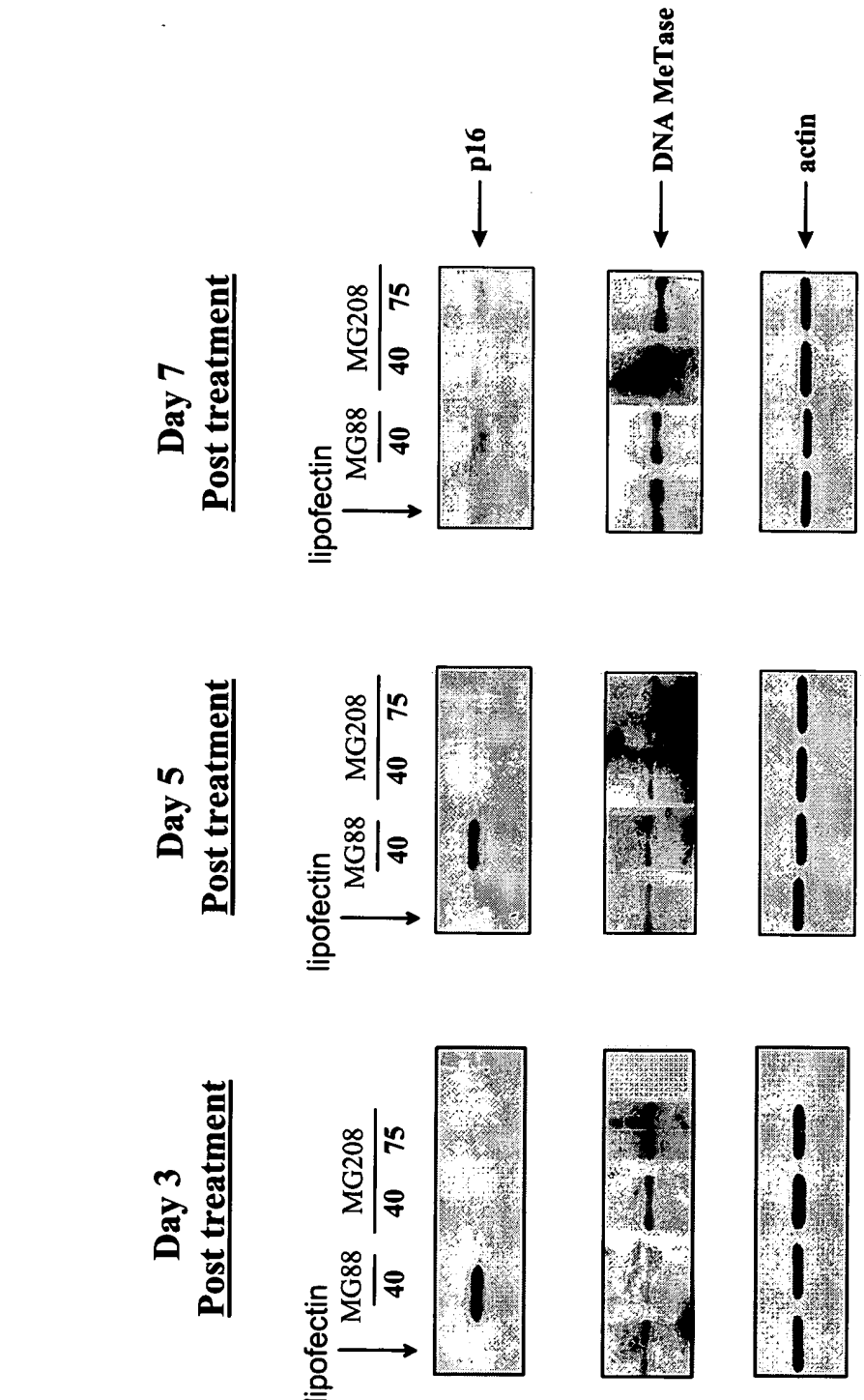

Day 3
Post treatment
Day 5
Post treatment
Day 7
Post treatment
lipofectin
MG88
MG208
40
40
75
p16
DNA MeTase
actin

FIG. 5

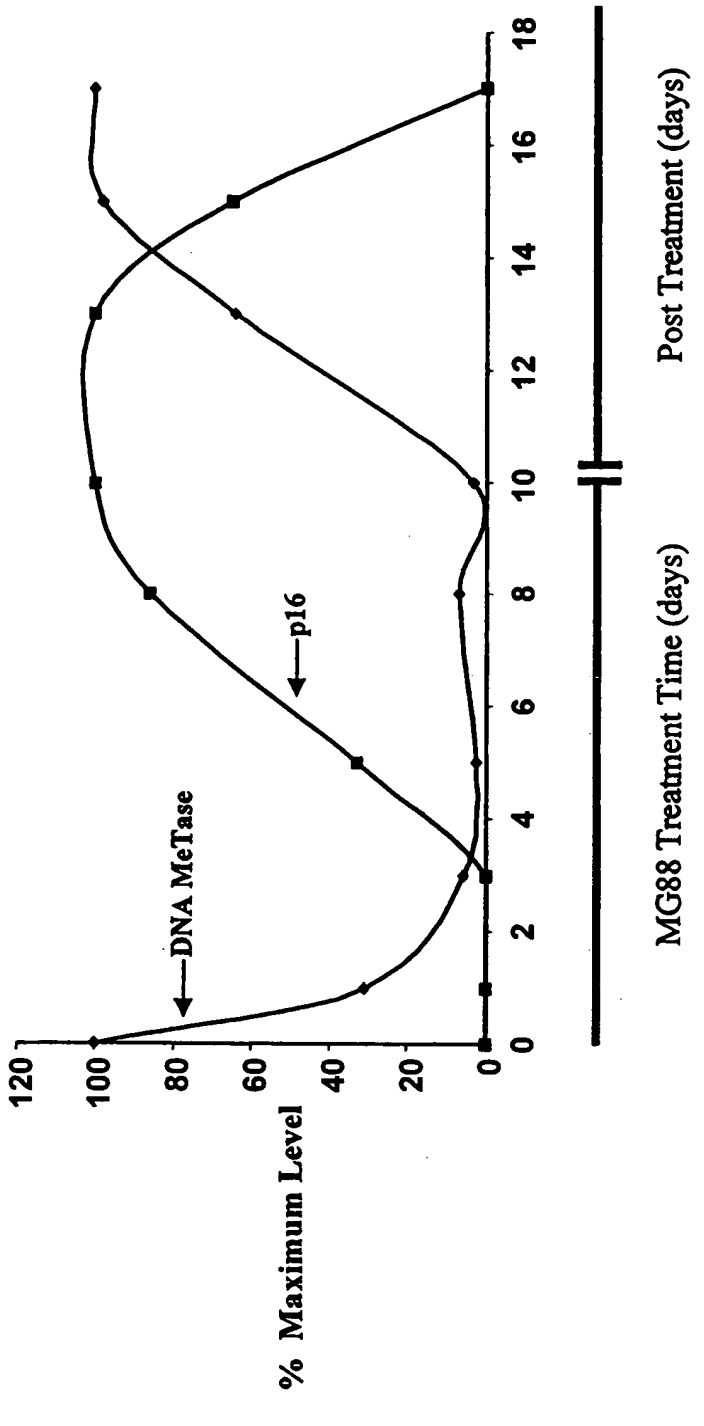

% Maximum Level
120
100
80
60
40
20
0
0
2
4
6
8
10
12
14
16
18
DNA MeTase
p16
MG88 Treatment Time (days)
Post Treatment (days)

FIG. 6

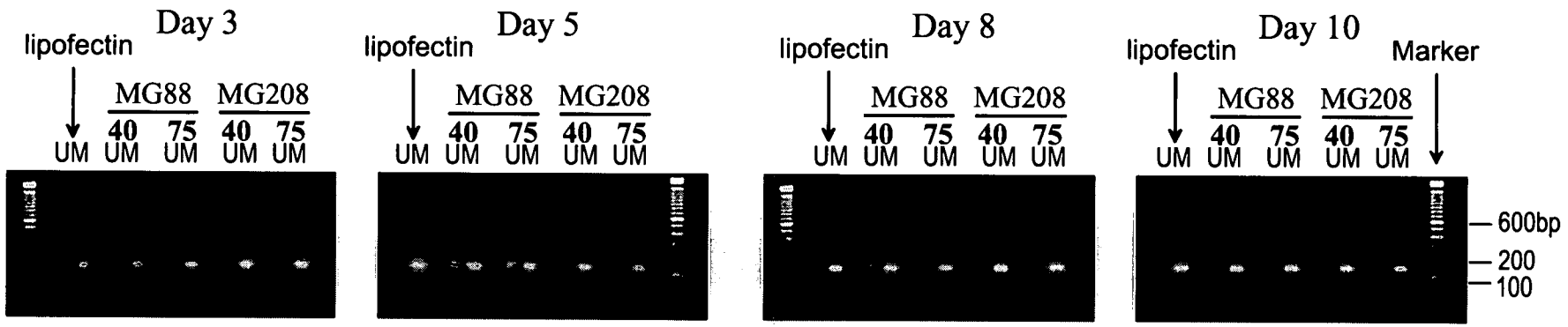
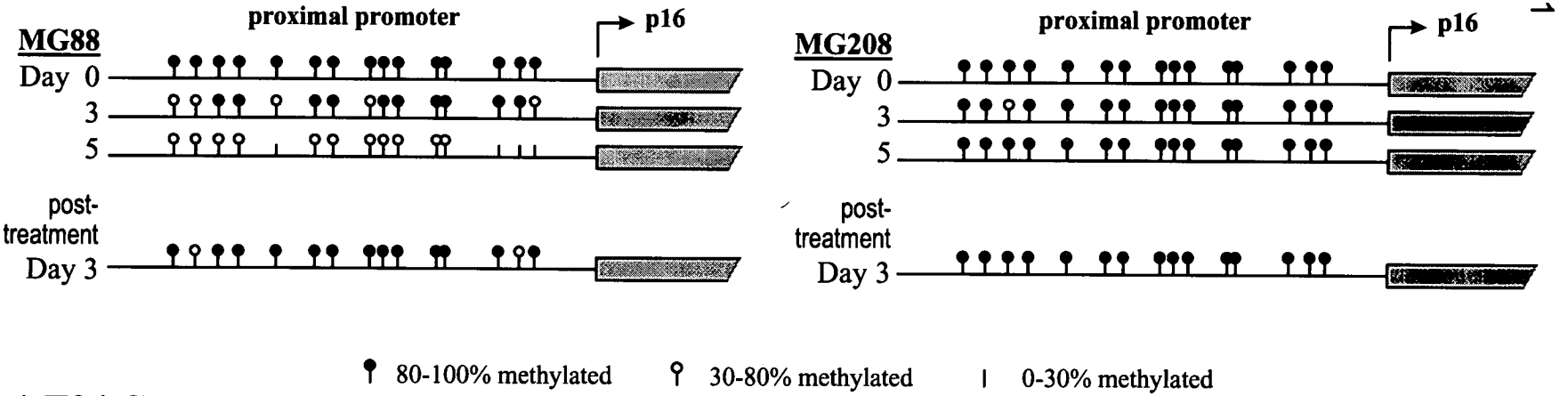


FIG. 7



*** T24 Cells**

FIG. 8

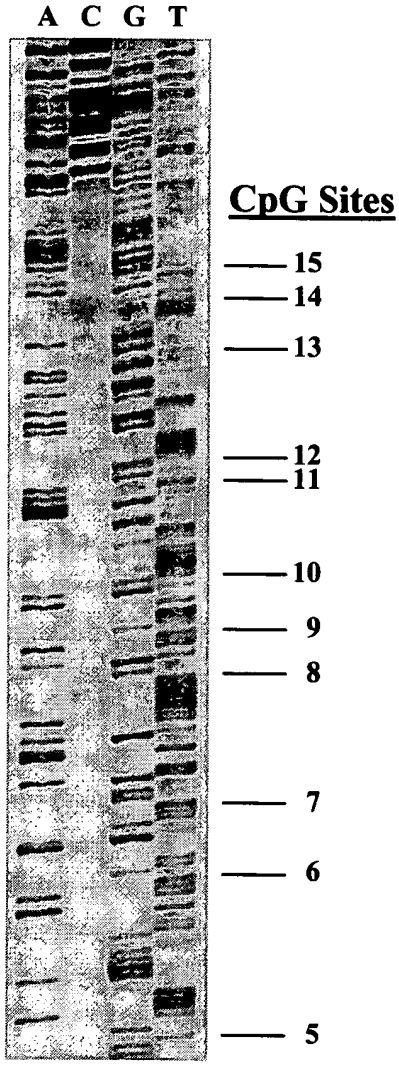


FIG. 9A

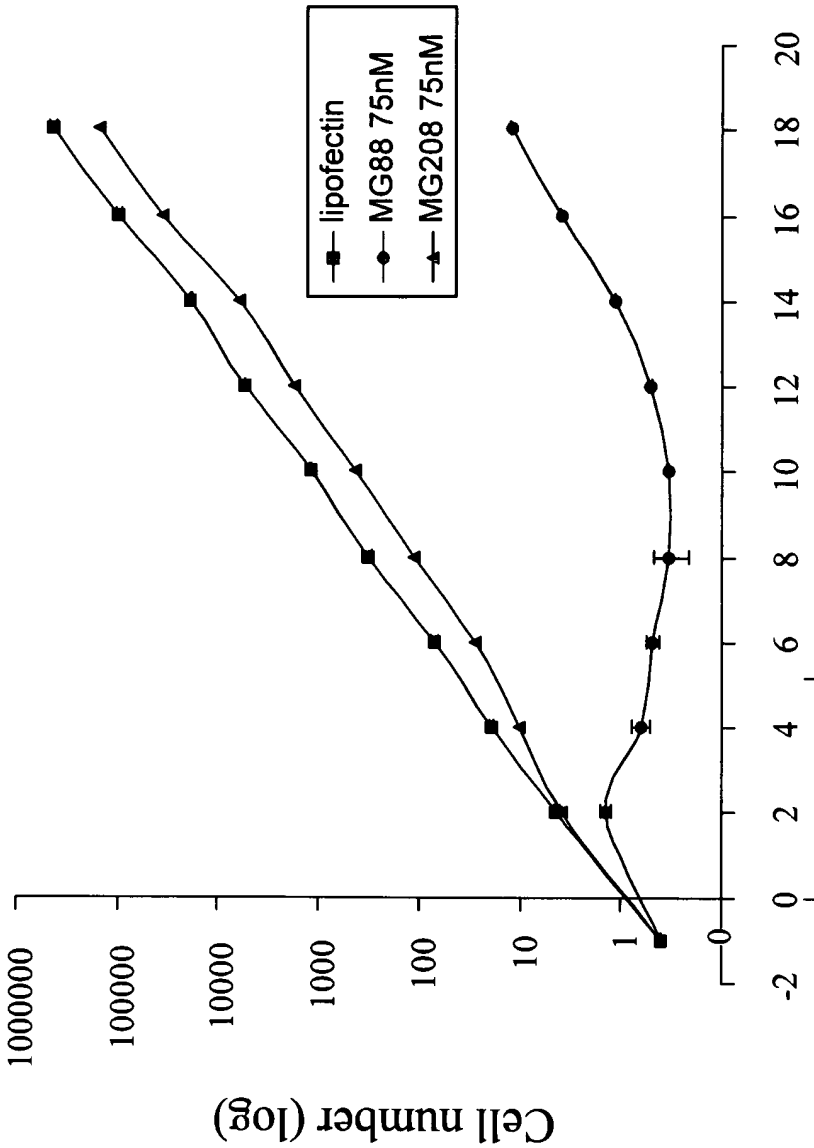

Cell number (log)
1000000
100000
10000
1000
100
10
1
-2
0
2
4
6
8
10
12
14
16
18
20
TIME OF TREATMENT
TIME (DAYS)
lipofectin
MG88 75nM
MG208 75nM

FIG. 9B

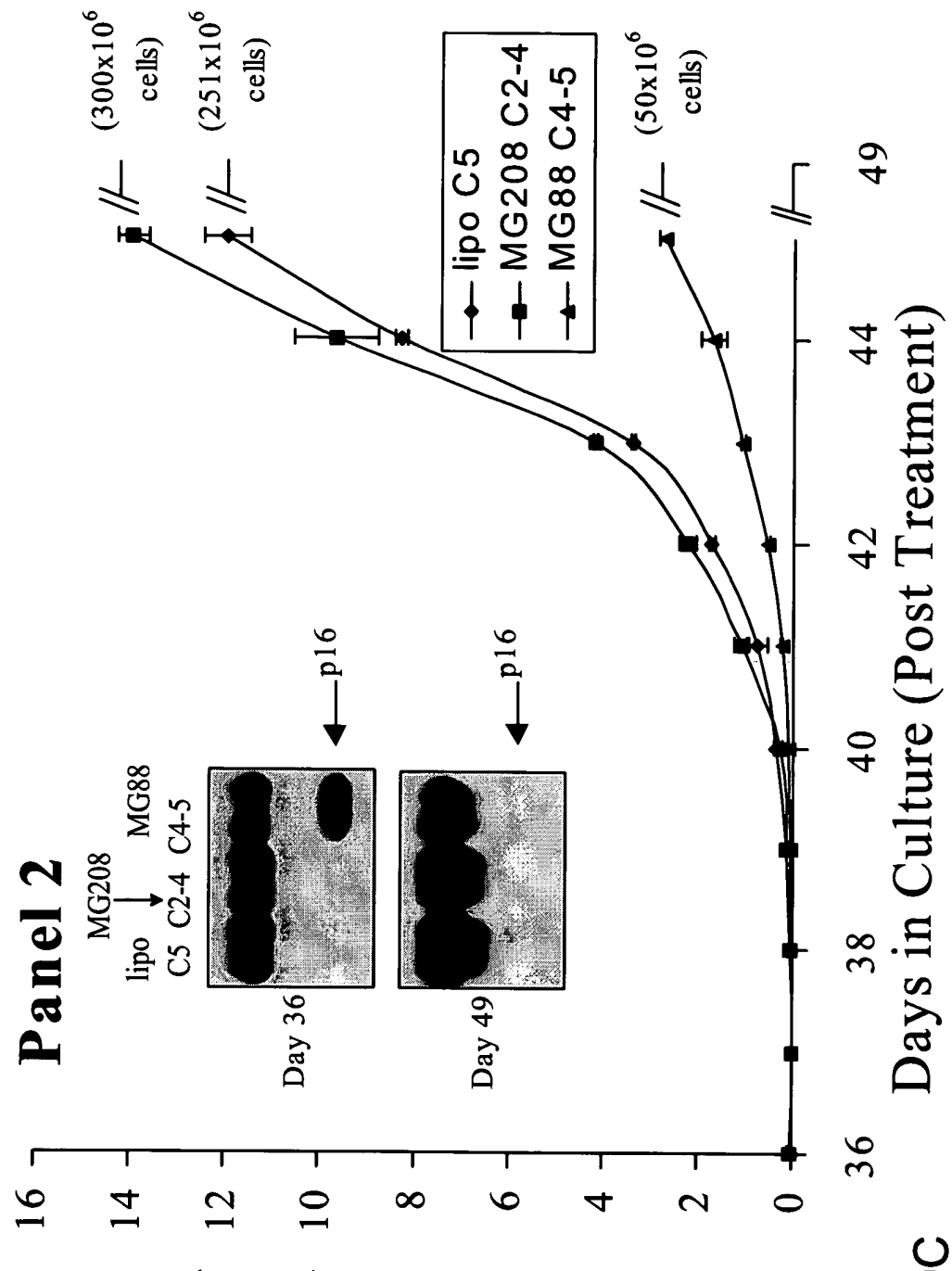

Panel 2
MG208
lipo
C5
MG88
C2-4
C4-5
p16
Day 36
p16
Day 49
(300x10^6 cells)
(251x10^6 cells)
(50x10^6 cells)
lipo C5
MG208 C2-4
MG88 C4-5
Cell number (x10^6)
Days in Culture (Post Treatment)
0
2
4
6
8
10
12
14
16
36
38
40
42
44
49

FIG. 9C

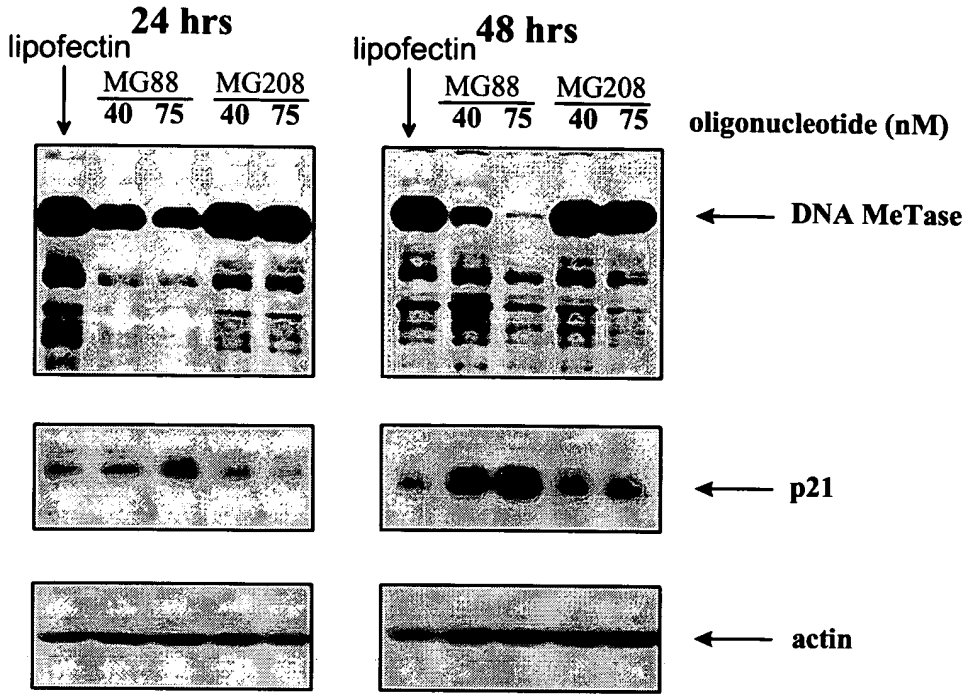


FIG. 10A

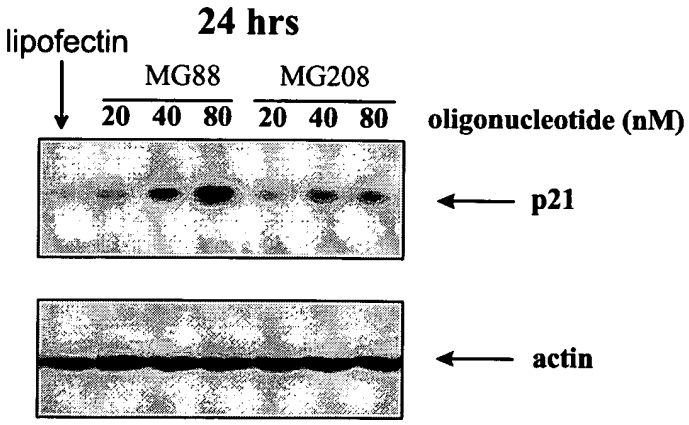


FIG. 10B

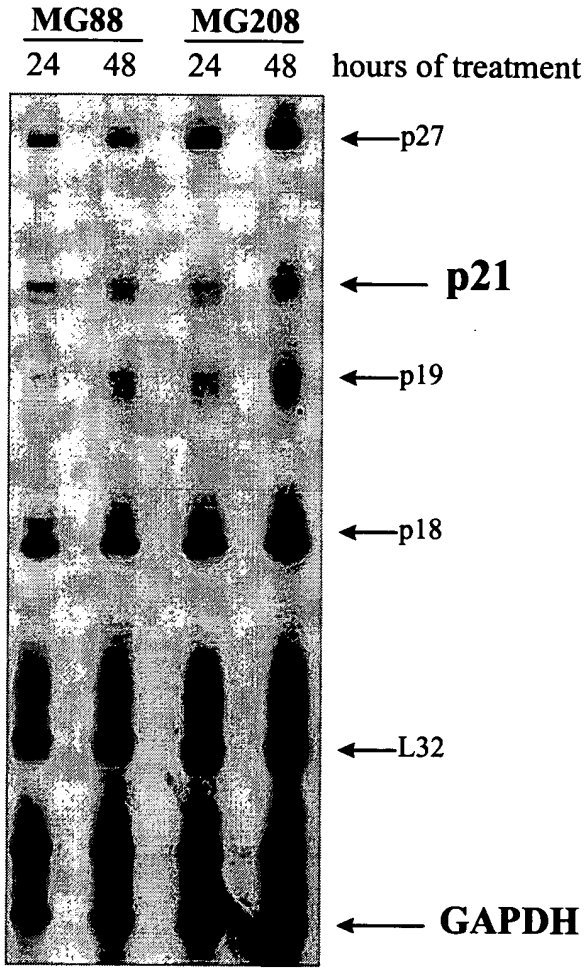
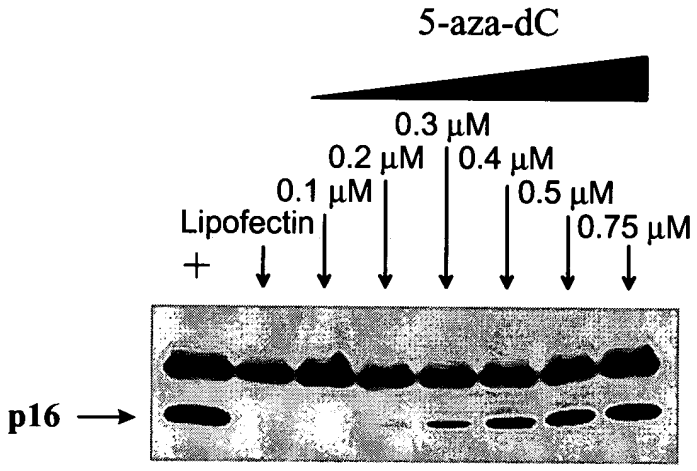

MG88
MG208
24 48 24 48 hours of treatment
p27
p21
p19
p18
L32
GAPDH

FIG. 11

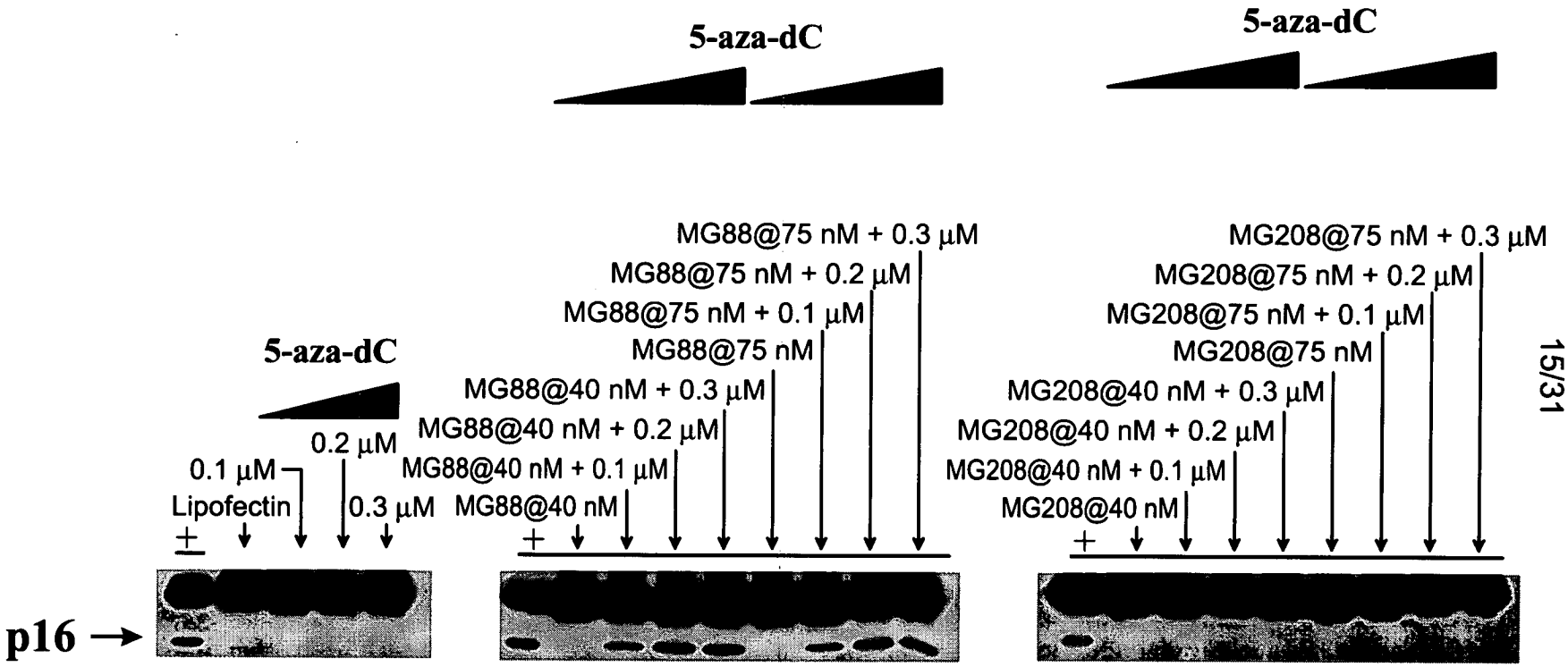
p16 reactivation in T24 cells by 5-aza-deoxycytidine treatment



T24 cells were plated and treated for three days with varying concentrations of 5aza-dC. The p16 protein was immunoprecipitated from celllysates and a Western analysis was performed.

FIG. 12

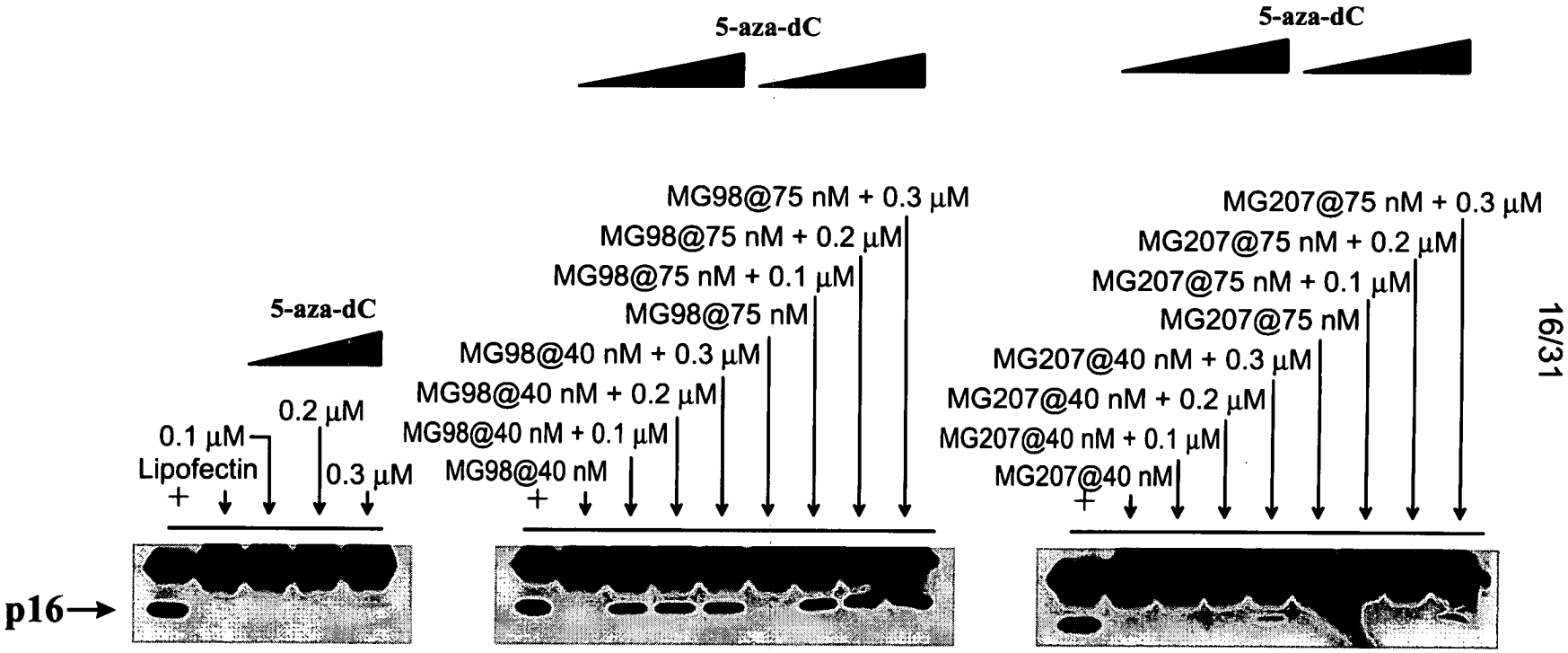
Synergistic reactivation of p16 in T24 cells by treatment with antisense to DNA methyltransferase (MG88) and 5-aza-deoxycytidine.



T24 cells were plated and transfected with either MG88 or MG208 and treated with varying concentrations of 5-aza-dC every day for three days. The p16 protein was immunoprecipitated from cell lysates and a Western analysis was performed.

FIG. 13

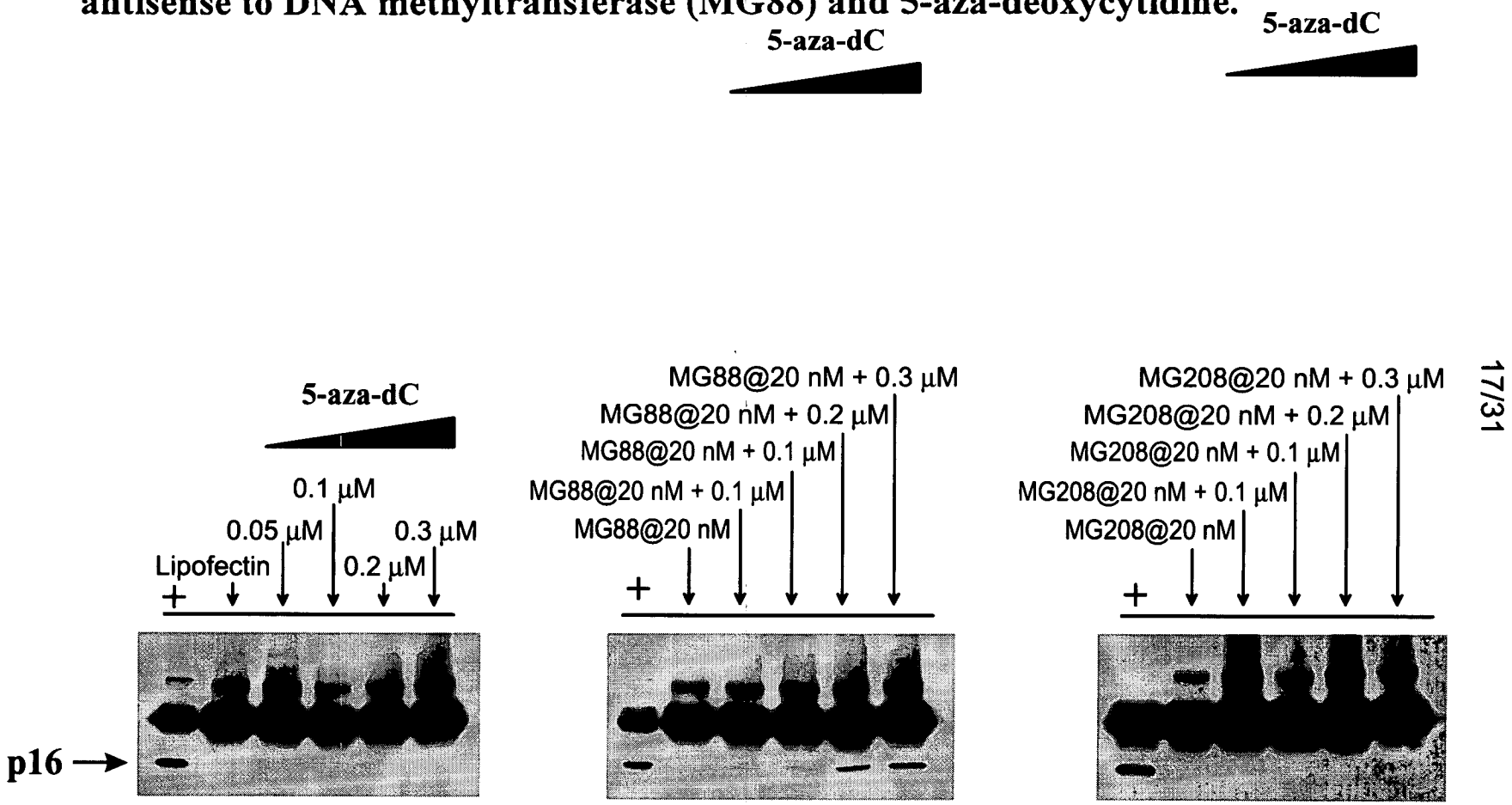
Synergistic reactivation of p16 in T24 cells by treatment with antisense to DNA methyltransferase (MG98)and 5-aza-deoxycytidine.



T24 cells were plated and transfected with either MG98 or MG207 and treated with varying concentrations of 5-aza-dC every day for three days. The p16 protein was immunoprecipitated from cell lysates and a Western analysis was performed.

FIG. 14

Synergistic reactivation of p16 in T24 cells by treatment with low dose antisense to DNA methyltransferase (MG88) and 5-aza-deoxycytidine.



T24 cells were plated and transfected with either MG88 or MG 208 and treated with varying concentrations of 5-aza-dC every day for three days. The p16 protein was immunoprecipitated from cell lysates and a Western analysis was performed.

FIG. 15

SYNERGISTIC INHIBITION OF T24 CELL GROWTH BY TREATMENT WITH ANTISENSE TO DNA METHYLTRANSFERASE (MG98) AND 5-aza-dC.

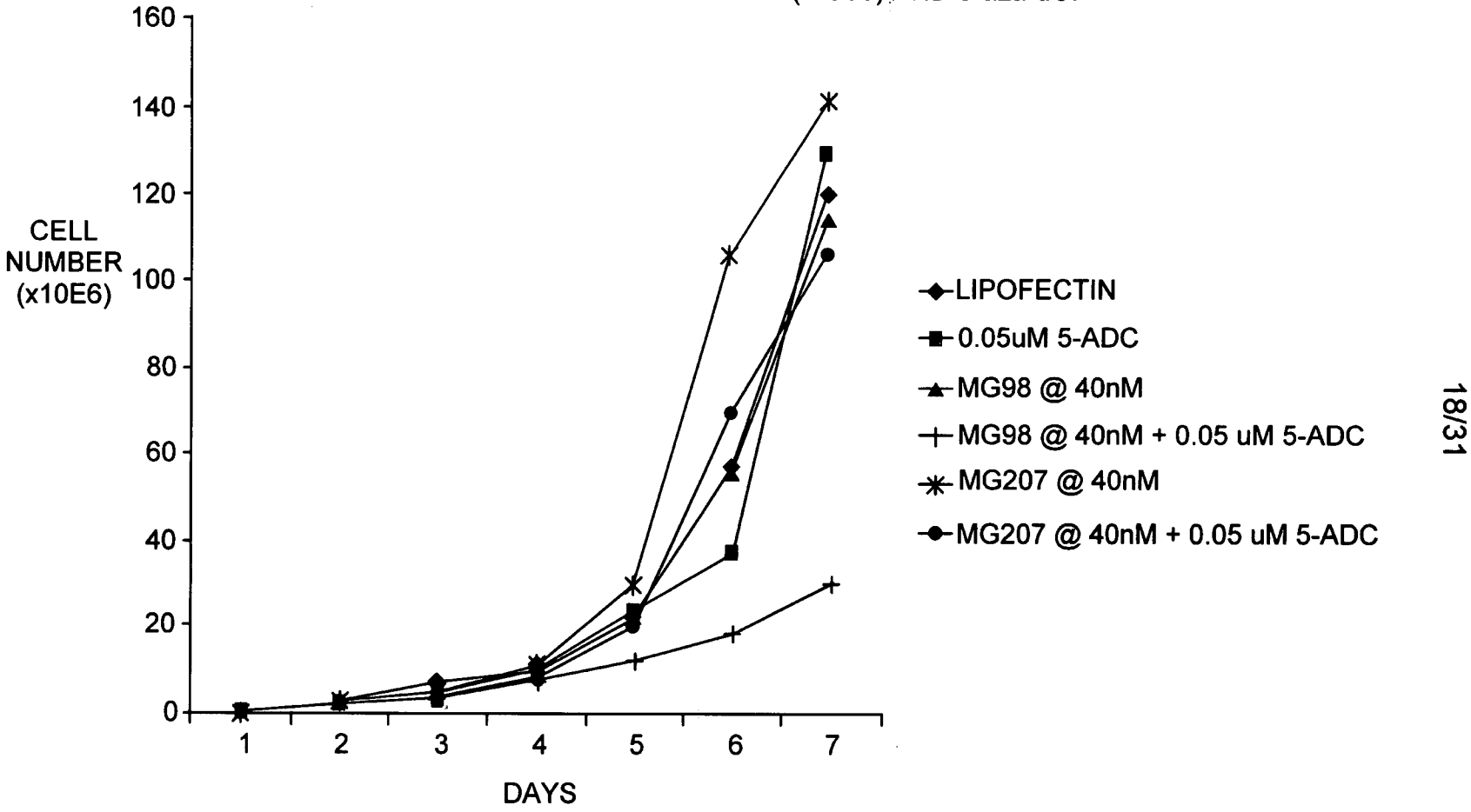


FIG. 16

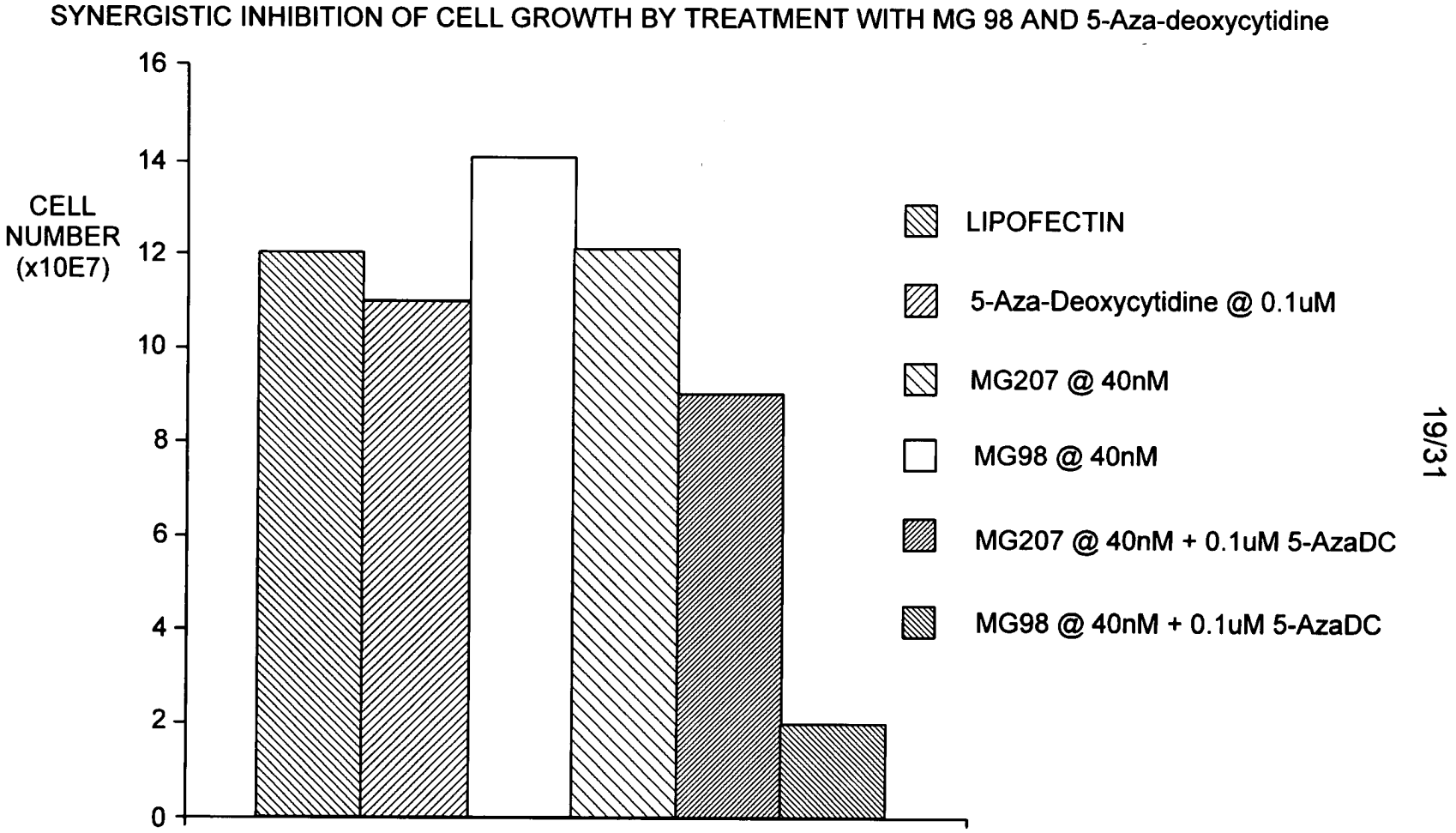

SYNERGISTIC INHIBITION OF CELL GROWTH BY TREATMENT WITH MG 98 AND 5-Aza-deoxycytidine
CELL NUMBER (x10E7)
16
14
12
10
8
6
4
2
0
LIPOFECTIN
5-Aza-Deoxycytidine @ 0.1uM
MG207 @ 40nM
MG98 @ 40nM
MG207 @ 40nM + 0.1uM 5-AzaDC
MG98 @ 40nM + 0.1uM 5-AzaDC

FIG. 17

SYNERGISTIC INHIBITION OF A549 CELL GROWTH BY TREATMENT WITH ANTISENSE TO DNA METHYLTRANSFERASE (MG98) AND 5-aza-dC.

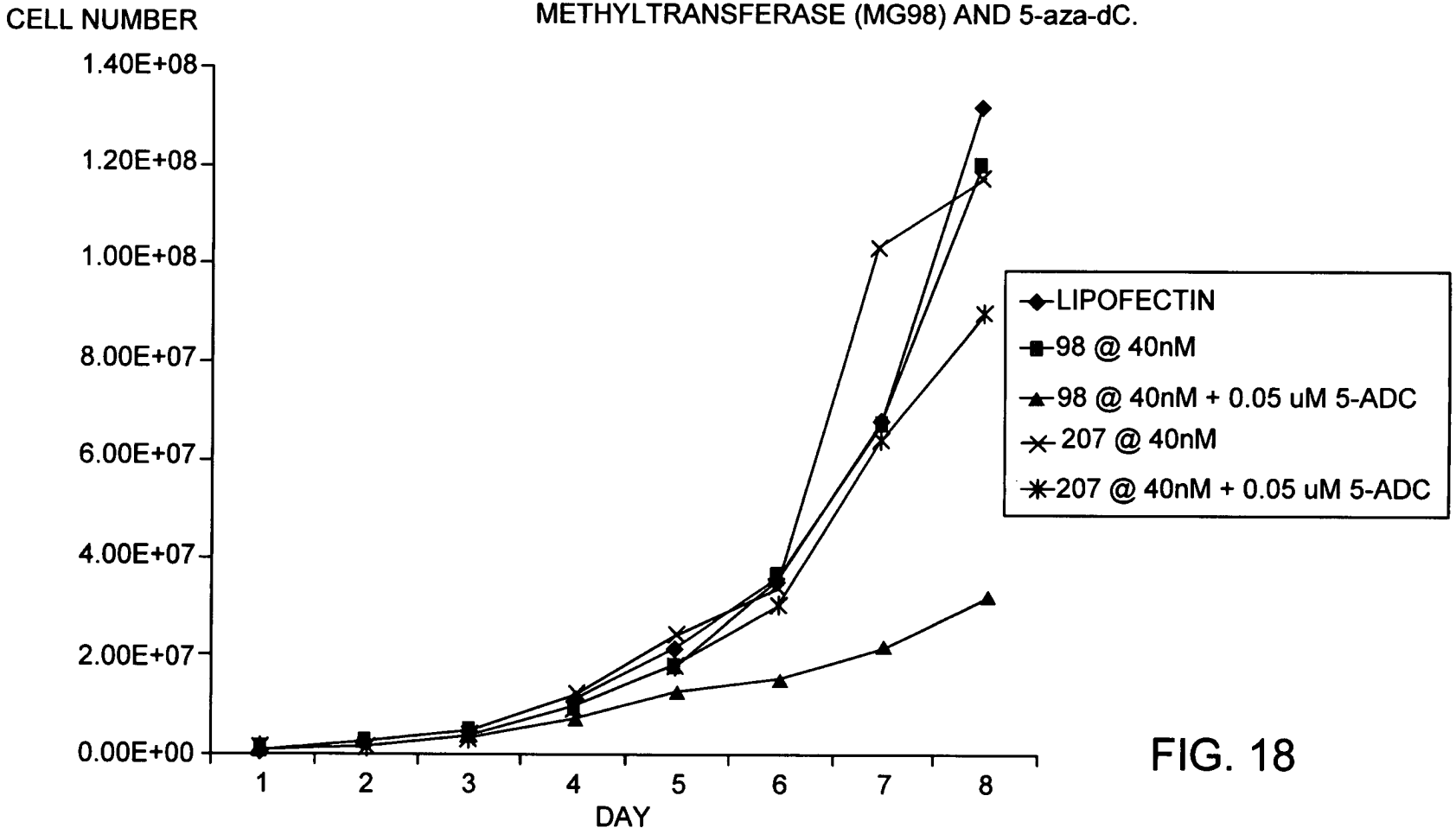


FIG. 18

IN VIVO SYNERGISTIC ANTITUMOR ACTIVITY OF ANTISENSE TO HUMAN DNA METHYLTRANSFERASE (MG98) COMBINED WITH A SMALL MOLECULE IN HUMAN COLON CANCER MODEL COLO 205.

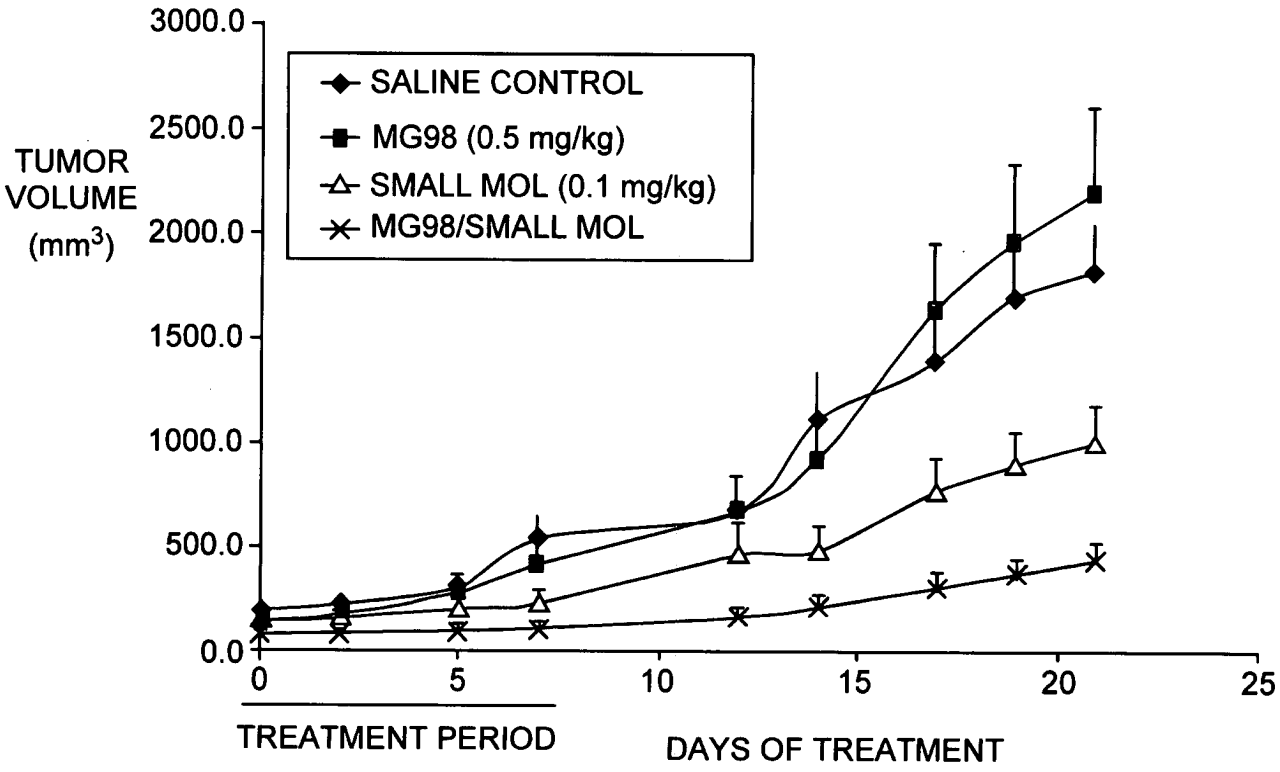


FIG. 19

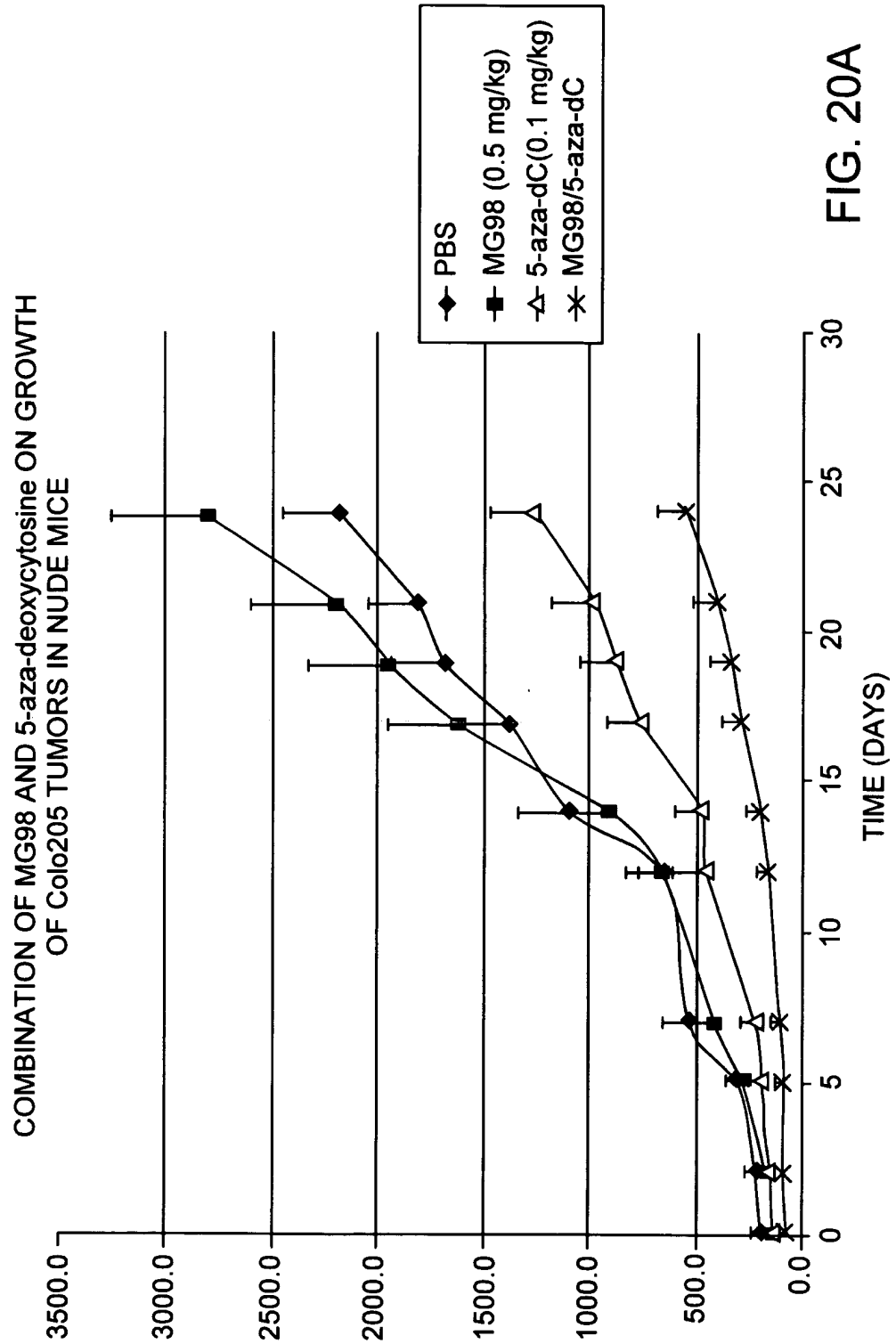
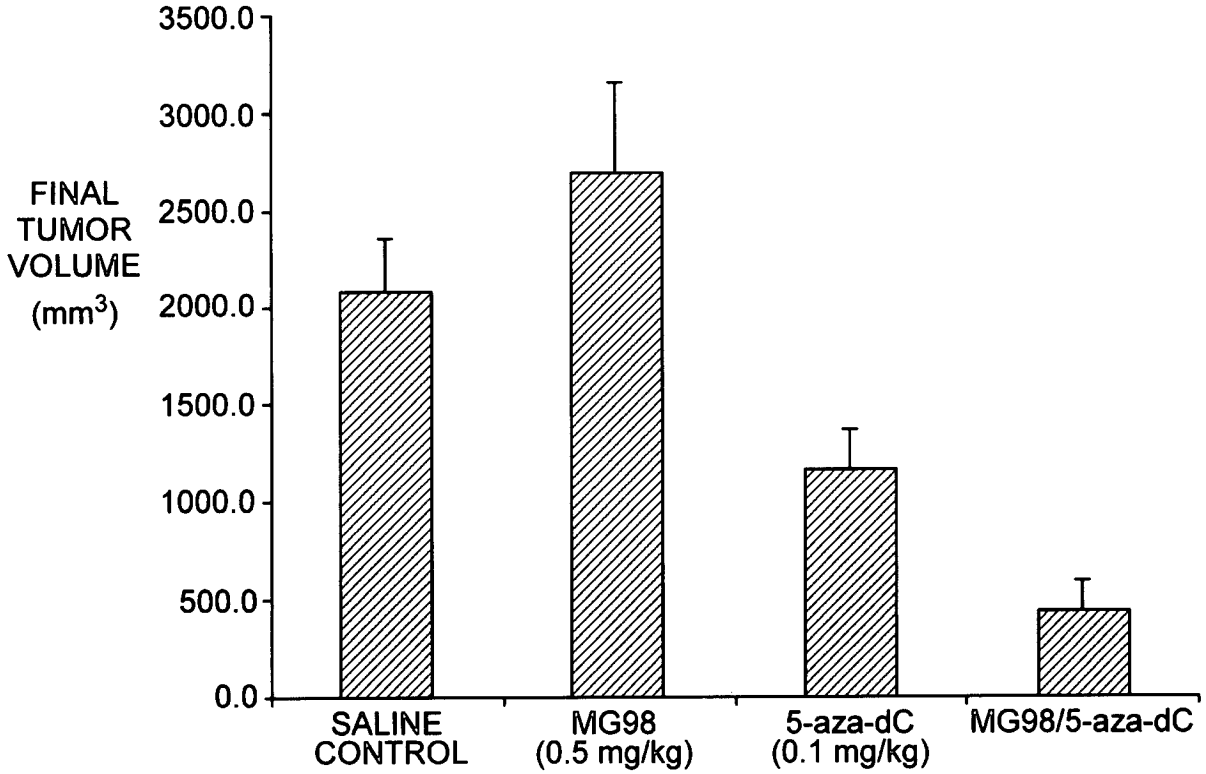

COMBINATION OF MG98 AND 5-aza-deoxycytosine ON GROWTH OF Colo205 TUMORS IN NUDE MICE
TUMOR VOLUME (mm3)
3500.0
3000.0
2500.0
2000.0
1500.0
1000.0
500.0
0.0
0
5
10
15
20
25
30
TIME (DAYS)
PBS
MG98 (0.5 mg/kg)
5-aza-dC(0.1 mg/kg)
MG98/5-aza-dC

FIG. 20A

FIG. 20B

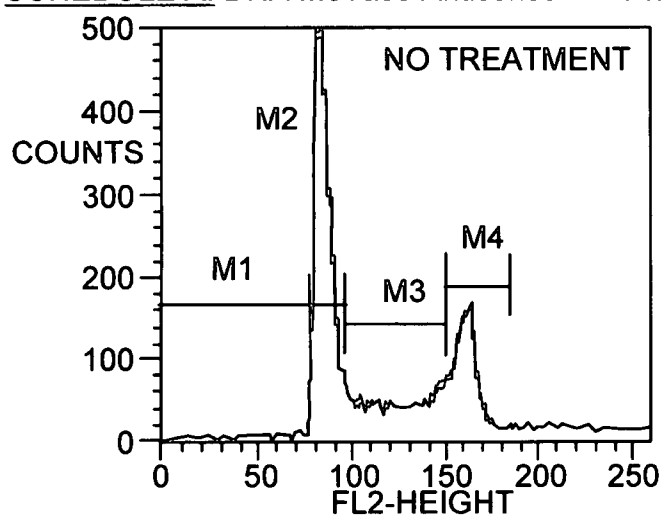
IN VIVO SYNERGISTIC ANTITUMOR ACTIVITY OF ANTISENSE TO HUMAN DNA METHYLTRANSFERASE (MG98) COMBINED WITH 5-aza-2-deoxycytidine IN HUMAN COLON CANCER MODEL COLO 205.

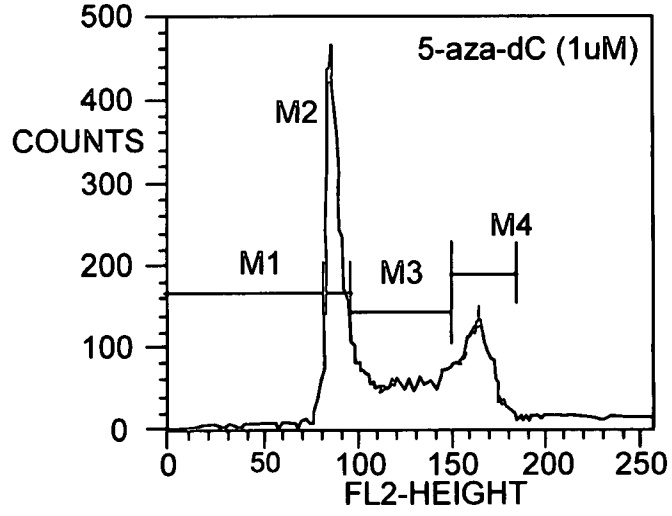


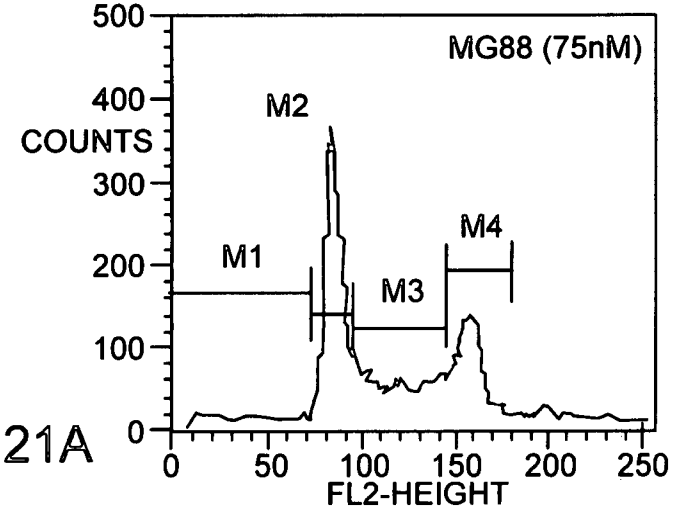
ANTITUMOR ACTIVITY OF COMBINATION OF MG98 AND 5-aza-2-deoxycytidine. GROUPS ARE: SALINE CONTROL, MG98 (0.5mg/kg/day), 5-aza-2-deoxycytidine (0.1 mg/kg/day), MG98 (0.5 mg/kg/day) AND 5-aza-2-deoxycytidine (0.1 mg/kg/day). GROUPS CONSISTED OF SIX ANIMALS EACH. ERROR BARS REPRESENT SEM. GROUP MG98/5-aza-dC WAS STATISTICALLY DIFFERENT ($p<0.05$) FROM BOTH SALINE TREATED GROUP AND FROM 5-aza-dC TREATED GROUP. GROUP MG98 WAS NOT SIGNIFICANTLY DIFFERENT THAN SALINE CONTROL GROUP.

SCHEDULE INDEPENDENT INHIBITION OF CELL CYCLE PROGRESSION BY COMBINATION OF DNA MeTase Antisense inhibitor (MG88) AND DNA MeTase Small Molecule Inhibitor (5-aza-dC).

SCHEDULE A: DNA MeTase Antisense Inhibitor (MG88) followed by Small Molecule Inhigitor (5-aza-dc)







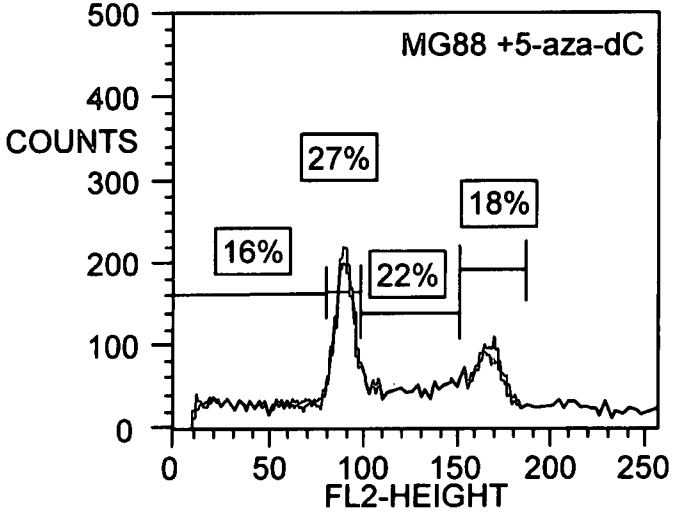


FIG. 21A

FIG. 21A

FIG. 21B

FIG. 21

SCHEDULE B: SMALL MOLECULE INHIBITOR (5-aza-dC) followed by DNA MeTase Antisense Inhibitor (MG88)

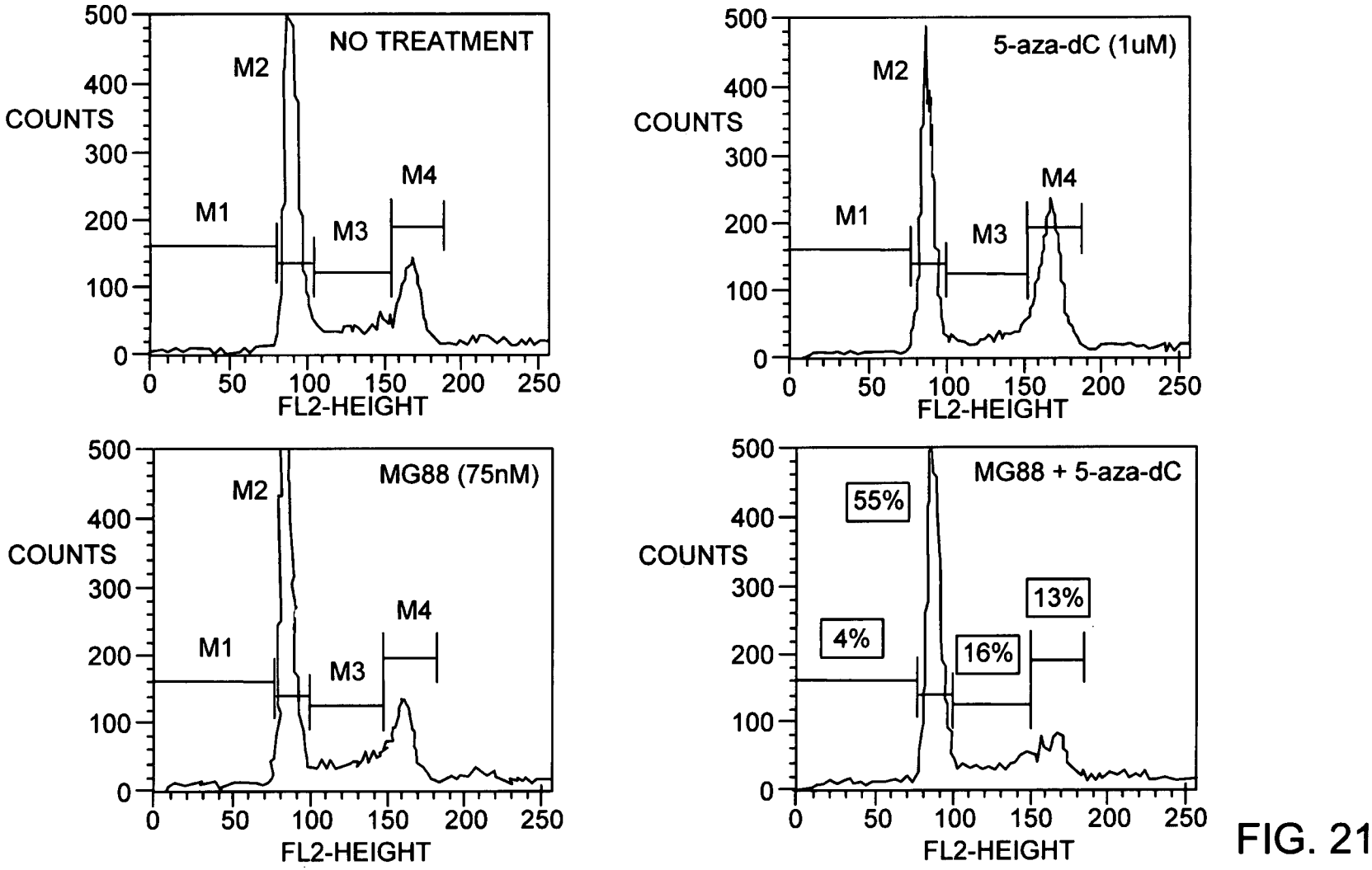


FIG. 21B

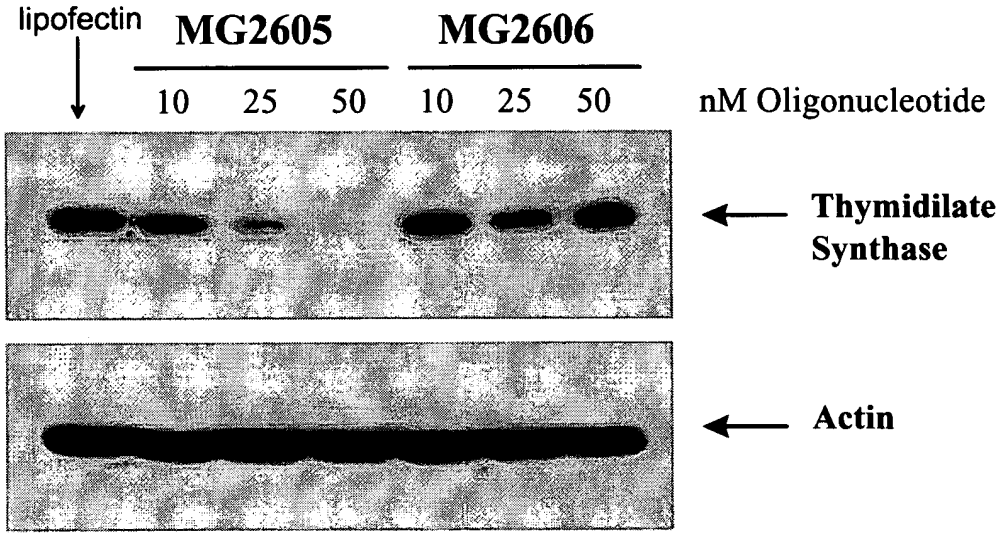
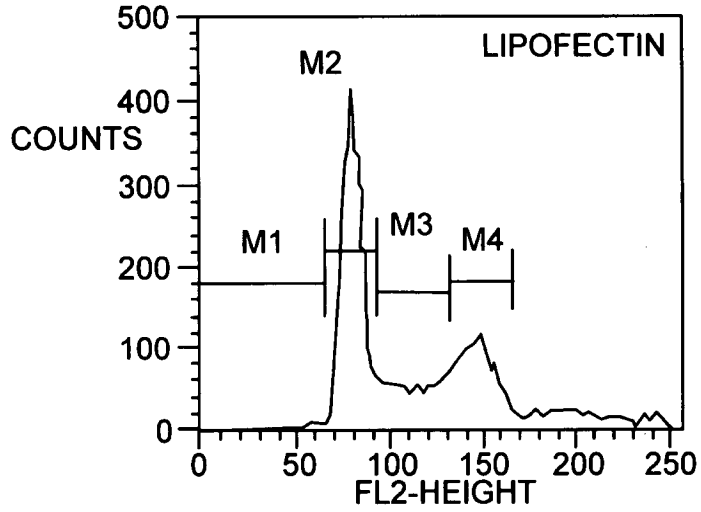

lipofectin
MG2605
MG2606
10 25 50 10 25 50
nM Oligonucleotide
Thymidilate Synthase
Actin

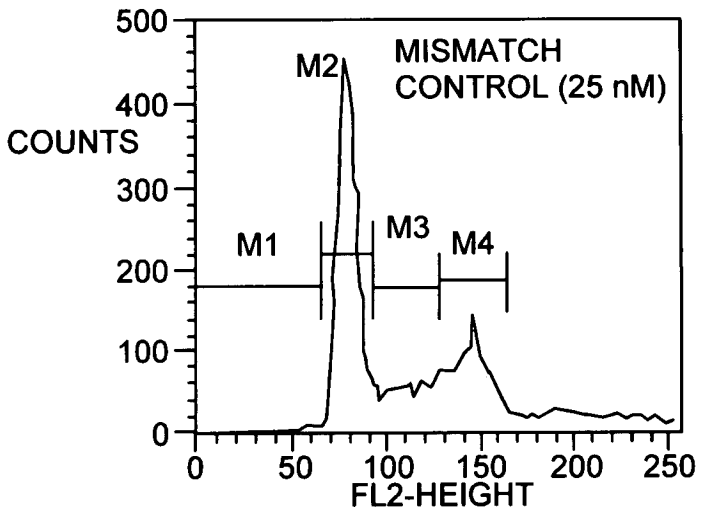
FIG. 22

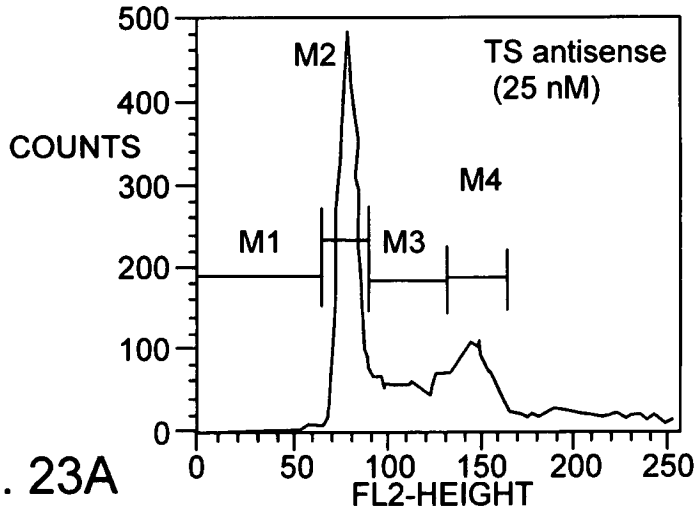
FIG. 23A

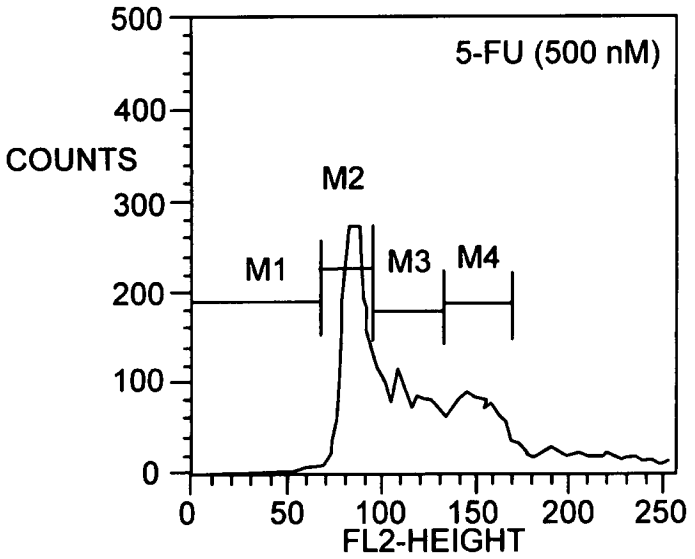
FIG. 23B

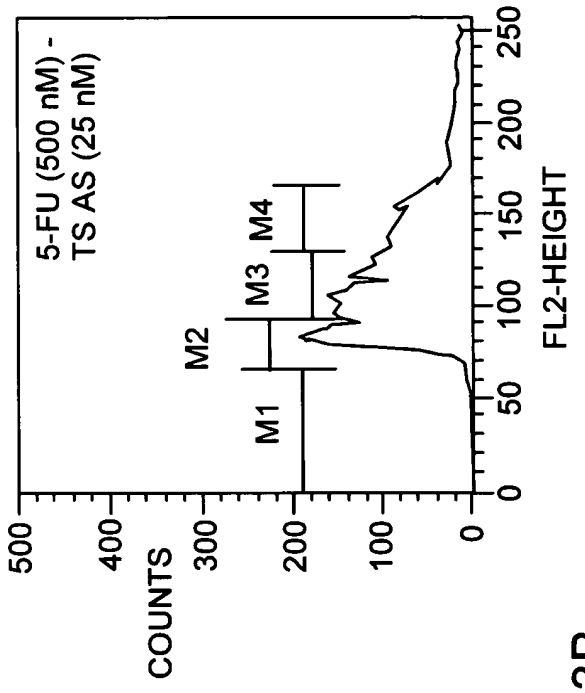
FIG. 23










5-FU (500 nM) -
TS AS (25 nM)
M1
M2
M3
M4
COUNTS
FL2-HEIGHT
0
100
200
300
400
500
50
150
250

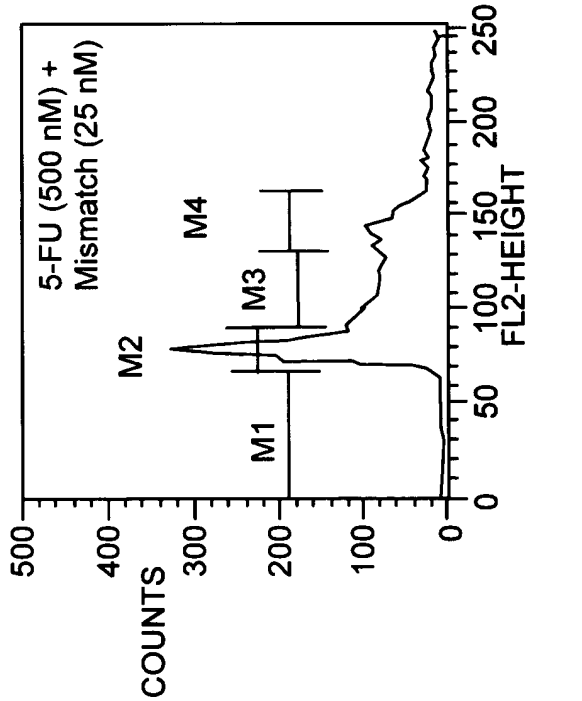
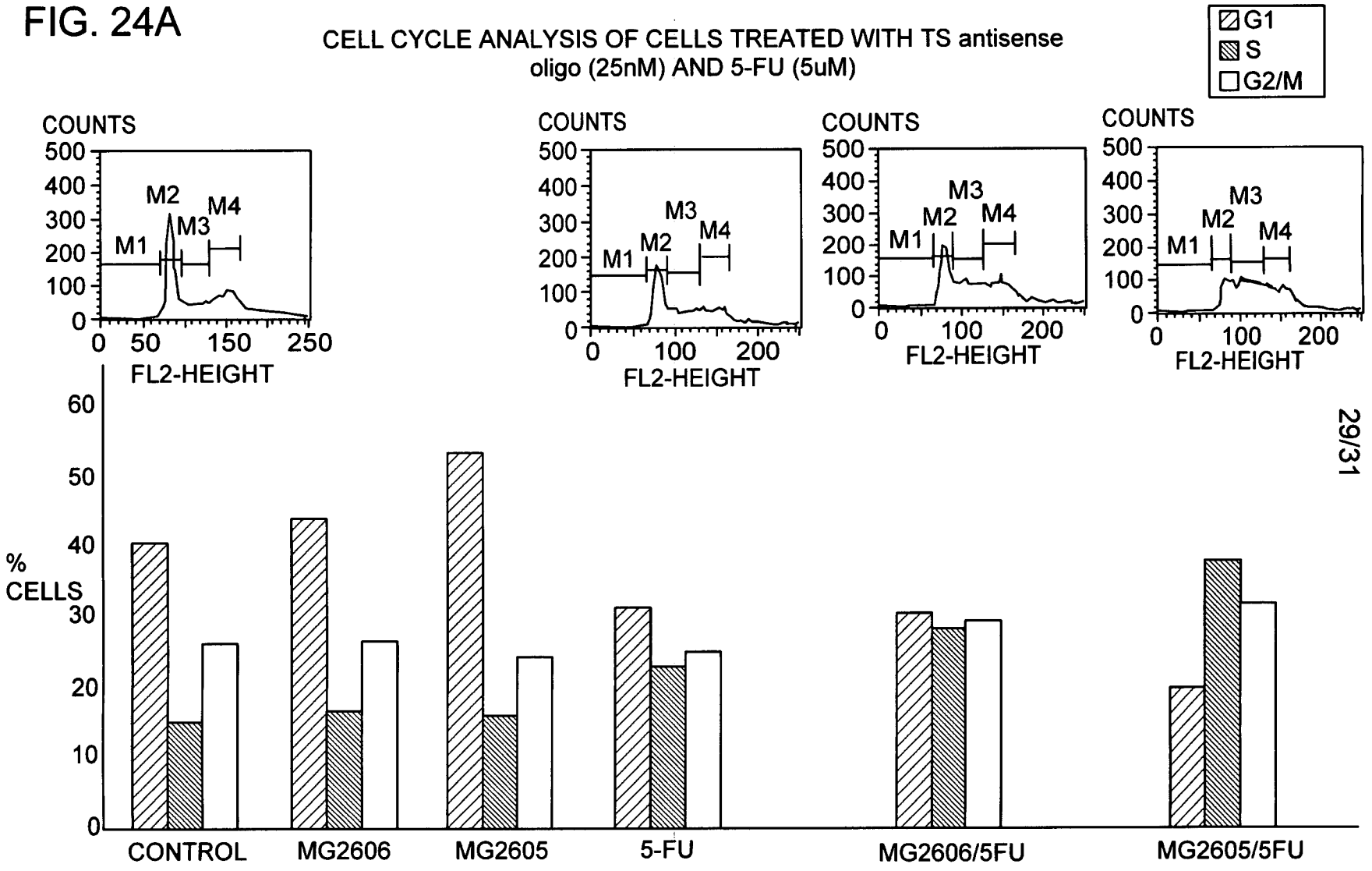

5-FU (500 nM) +
Mismatch (25 nM)
M1
M2
M3
M4
COUNTS
FL2-HEIGHT
0
100
200
300
400
500
50
150
250

FIG. 23B

FIG. 24A


CELL CYCLE ANALYSIS OF CELLS TREATED WITH TS antisense oligo (25nM) AND 5-FU (5uM)
G1
S
G2/M
COUNTS
M1
M2
M3
M4
FL2-HEIGHT
% CELLS
CONTROL
MG2606
MG2605
5-FU
MG2606/5FU
MG2605/5FU

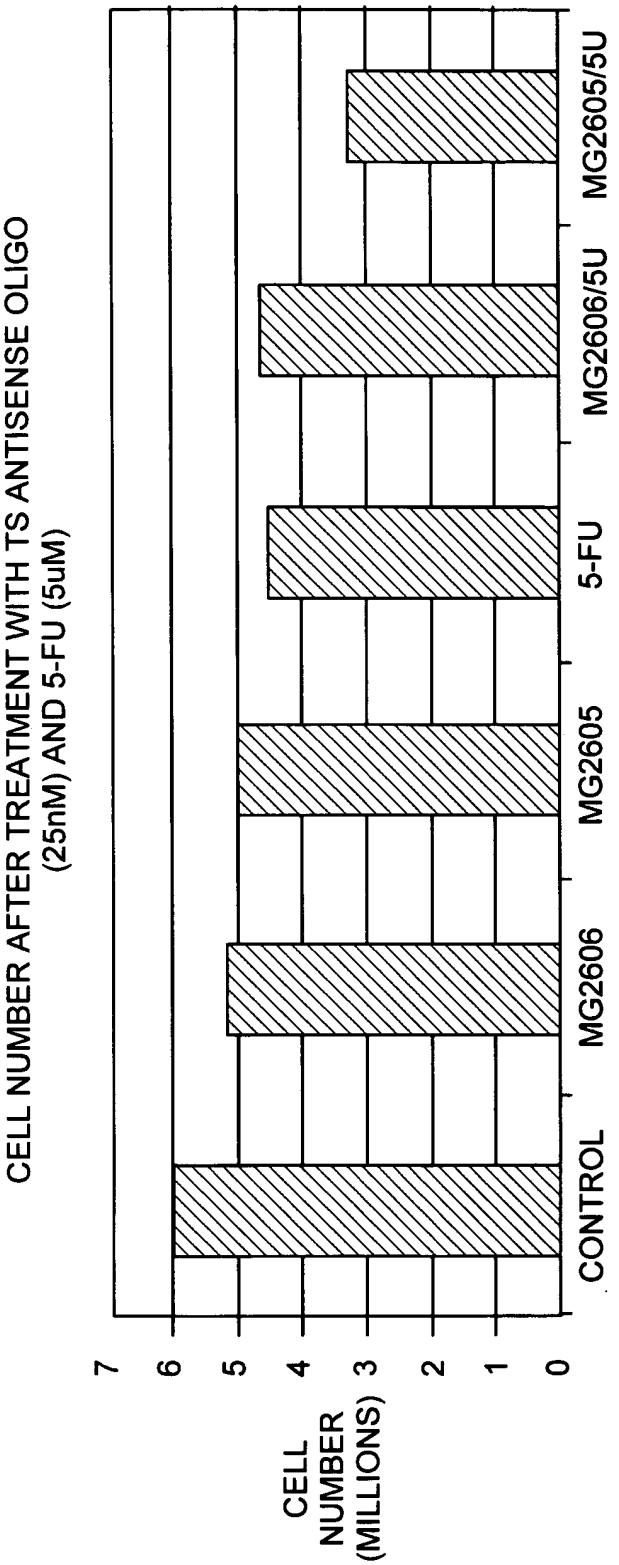

CELL NUMBER AFTER TREATMENT WITH TS ANTISENSE OLIGO
(25nM) AND 5-FU (5uM)
CELL NUMBER (MILLIONS)
0
1
2
3
4
5
6
7
CONTROL
MG2606
MG2605
5-FU
MG2606/5U
MG2605/5U

FIG. 24B

Synergistic Induction of p21WAF1/CIP by Combination of HDAC Antisense and TSA

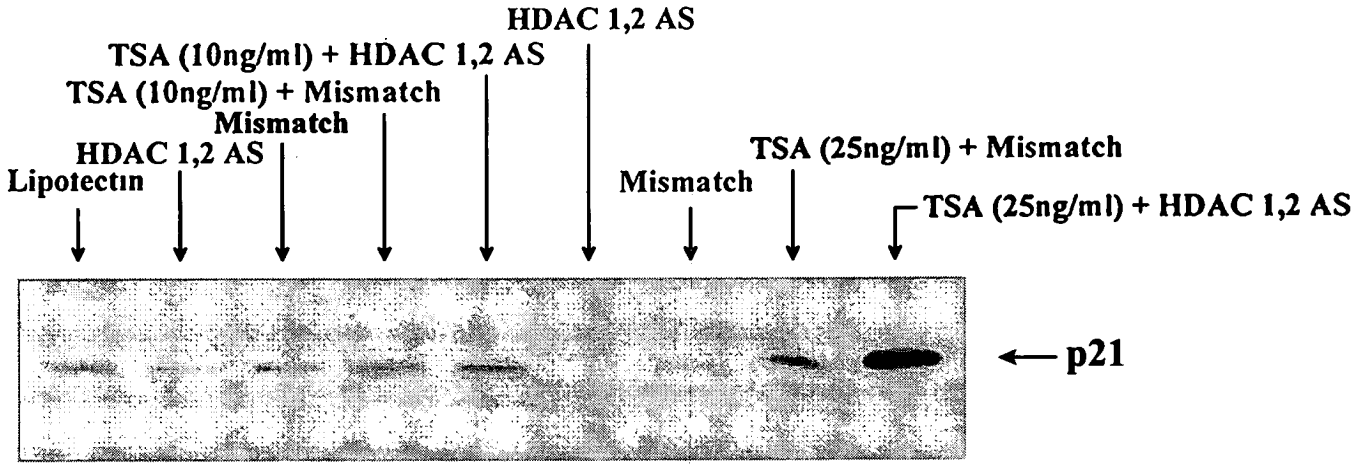


FIG. 25